AR201-13817B

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation	Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-	Study Number	1
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)	Completed:	

Revision Date: 12/10/01

Test Substance

Remarks: The test substance was a composite of the commercial TBBPA products produced by Albemarle Corporation, Dead Sea Bromine Group, and Great Lakes Chemical Corporation.

Chemical Category

Method

>> Method/Guideline followed

EPA OPPTS Method 870.3700, OECD 414

>> GLP: Yes

>> Year study performed: 2001

>> Species: rat

>> Strain: **Mammal strai:** CD

>> Sex: F

>> Number of males per dose: 0

>> Number of females per dose: 25

>> Route of Administration: Oral, gavage in corn oil

>> Days of Gestation: 0-19

>> Frequency of treatment: once/day

>> Doses: 0, 100, 300, 1000 mg/kg-bw

>> Control Group: Yes **Concurrent control**

>> Statistical Method

See results.

Remarks for Method

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	1
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

This study consisted of 3 treatment groups and 1 vehicle (corn oil) control group (25 mated female rats/group). Female CD rats were mated in-house and received TBBPA at dose levels of 0, 100, 300 and 1000 mg/kg/d by gavage in corn oil once daily at a constant volume of 5 ml/kg. The control animals received the vehicle at the same volume and dosing regimen as the treated groups. Dosing initiated on Day 0 of gestation and continued through to include Day 19 of gestation. The day on which evidence of mating was observed was considered Day 0 of gestation. Observations of the dams included clinical signs, gestational body weights, food consumption. Females were euthanized on Day 20 of gestation and given a postmortem macroscopic examaination. Gross lesions were saved in 10% neutral buffered formalin for possible future examinaiton. Garavid uterine weights and liver weights were recorded. Litters were delivered by cesarean section. The total number of corpora lutea, uterine implantations, early and late resorption, viable and nonviable fetuses, and the sex and individual weights of fetuses were recorded. All fetuses were given a gross external examination for malformations and variations. Approximately one-half of the fetuses in each litter were fixed in Bouin's solution, and the remaining fetuses were skinned and preserved in alcohol. Bouin's-fixed fetuses from control and all treated groups were examined for visceral abnormalities (freehand razor blade sectioning procedure), and the remaining fetuses from all gorups were stained with Alizarin Red S and Alcian Blue and evaluated for skeletal/cartilaginous malformations and ossification variations. The maternal Day 20 gestation examinations and cesarean sections and subsequent fetal evaluations were preformed blind to treatment.

Results

>> Maternal Precision/NOAEL =

>> Maternal NOAEL dose 1000 **>> Unit used** mg/kg-bw

>> Maternal NOAEL effect Salivation due to taste of test article.

>> Maternal Precision/LOAEL >

>> Maternal LOAEL dose 1000 **>> Unit used** mg/kg-bw

>> Maternal LOAEL effect No adverse effects noted.

>> Developmental Precision/NOAEL =

>> Developmental NOAEL dose 1000 **>> Unit used** mg/kg-bw

>> Developmental NOAEL effect No adverse effects noted.

>> Developmental Precision/NOAEL >

>> Developmental LOAEL dose 1000 **>> Unit used** mg/kg-bw

>> Developmental LOAEL effect No adverse effects noted.

>> Actual dose

As given above.

>> Maternal data with dose level (with NOAEL value).

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	1
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

Only effect noted was salivation, believed due to method of administration (gavage) and taste of the test article.

>> Fetal data with dose level (with NOAEL value).

No effects noted.

>> Statistical results

See results.

Results Remark

Pretest analyses confirmed that the suspensions as prepared were homogeneous and stable for at least 14 days when stored refrigerated. Periodic analysis of dosing suspensions used in the study ranged from 88 to 113% of nominal and confirmed that animals received the appropriate dose levels.

No treatment-related mortality was seen. The death of 1 animal in the 300 mg/kg/d group on Gestation Day 5 was attributed to an intubation injury. All other animals survived to scheduled euthanasia.

Salivation was seen among the TBBPA-treated animals, occurring most frequenstly at the 300 and 1000 mg/kg/d dose levles. Because of its sporadic occurrence, this was not considered to represent a direct effect of treatment with TBBPA, but more likely was in response to the tste of residual amounts of test article on the dosing catheter. No other effects of treatment were seen from the clincial examinations, and no effect of treatment was evident from gestational parameters (body weight, body weight gain, or food consumption), uterine implantation data, liver weights, or necropsy findings. Likewise, no effect of treatment was evident from fetal body weights, fetal sex distribution, or from fetal external, visceral, or skeletal examinations.

Statistical methods included group pair-wise comparisons, Fisher's Exact Test, Arcsin-square-root transformation, descriptive statistics, and covariate analysis. The exact statistical test utilized was dependent on the end-point in question.

Conclusions

The NOAEL for maternal and developmental toxicity was 1000 mg TBBPA/kg/d, the highest dose level evaluated, administered on gestation days 0-19.

Data Quality

Reliability High

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	1
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

Data Reliability Remarks

This study was conducted according to current guidelines by a laboratory with considerable expertise.

Reference

>> Remarks

Schroeder, R. An oral prenatal developmental toxicity study with tetrabromobisphenol A in rats. Study No. 474-005. 2001. MPI Research, Mattawan, MI.

General

Study sponsored by the American Chemistry Council Brominated Flame Retardant Industry Panel.

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	2
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

Revision Date: 12/10/01

Test Substance

Remarks: TBBPA

Chemical Category

Method

>> Method/Guideline followed

Pre-dates OECD and EPA guidelines

>> GLP: Unknown

>> Year study performed: 1978

>> Species

rat

>> Strain | **Mammal strai:** CD

>> Sex: F

>> Number of males per dose: 0 | **>> Number of females per dose:** 5

>> Route of Administration: Oral

>> Days of Gestation: 6-15

>> Frequency of treatment: once daily

>> Doses: 0, 30, 100, 300, 1000, 3000 or 10,000 mg/kg-bw

>> Control Group: Yes | **Concurrent control**

>> Statistical Method

Not specified.

Remarks for Method

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	2
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

TBBPA was administered by gavage at dose levels of 0, 30, 300, 1000, 3000 or 10,000 mg/kg/d on gestation days 6-15 to groups of 5 Charles River CD female rats (15 weeks old). The rats were sacrificed on gestation day 20.

Results

>> Maternal Precision/NOAEL =

>> Maternal NOAEL dose 3000 **>> Unit used** mg/kg-bw

>> Maternal NOAEL effect None.

>> Maternal Precision/LOAEL =

>> Maternal LOAEL dose 5000 **>> Unit used** mg/kg-bw

>> Maternal LOAEL effect Death, loose stools.

>> Developmental Precision/NOAEL =

>> Developmental NOAEL dose 3000 **>> Unit used** mg/kg-bw

>> Developmental NOAEL effect None.

>> Developmental Precision/NOAEL =

>> Developmental LOAEL dose 3000 **>> Unit used** mg/kg-bw

>> Developmental LOAEL effect None.

>> Actual dose

As above.

>> Maternal data with dose level (with NOAEL value).

See Results

>> Fetal data with dose level (with NOAEL value).

See Results

>> Statistical results

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation	Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-	Study Number	2
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)	Completed:	

See Results

Results Remark

Three of 5 rats in the 10,000 mg/kg/d group died, while the remaining rats in this group showed a slight decrease in body weight gain between gestation days 6 and 15; green, soft stools; and an increase in matted hair in the anogenital area. There were no signs of toxicity in rats adminstered doses up to and including 3000 mg/kg/d. There were no differences in the mean numbers of viable or nonviable fetuses, resorptions, implantations or corpora lutea compared with the controls.

Conclusions

The maternal and fetal NOAEL for TBBPA in this study was 3000 mg/kg/d administered on gestation days 6-15.

Data Quality

Reliability Reasonable.

Data Reliability Remarks

This study is old and likely does not conform to today's guidelines. However, TBBPA's lack of toxicity in this study at doses <= 3,000 mg/kg-bw is consistent with the 2001 BFRIP study.

Reference

>> Remarks

Godenthal EI, Jessup DC and Roadwell DE (1978). Tetrabromobisphenol A (FMBP-4A) pilot teratology study in rats. IRDC, Mattawan, MI. As described in the 1995 WHO IPCS EHC Document No. 172., Geneva.

General

Sponsored by Great Lakes Chemical Corp.

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	3
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

Revision Date: 12/10/01

Test Substance

Remarks: TBBPA.

Chemical Category

Method

>> Method/Guideline followed

Not specified

>> GLP: Unknown

>> Year study performed: 1985

>> Species

rat

>> Strain | **Mammal strai:** Wistar

>> Sex: F

>> Number of males per dose: 0

>> Number of females per dose: 25

>> Route of Administration: Oral

>> Days of Gestation: 0-19

>> Frequency of treatment: once daily

>> Doses: 0, 280, 830, 2500 mg/kg/d

>> Control Group: Yes | **Concurrent control**

>> Statistical Method

Not available.

Remarks for Method

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	3
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

Pregnant Wistar rats were treated with TBBPA at dose levels of 0, 280, 830 or 2500 mg/kg/d on days 0-19 of gestation for fetal examination or to parturition for postnatal examination (21 days post-birth). Ceasarian sections were performed on day 20 of gestation.

Results

>> Maternal Precision/NOAEL =

>> Maternal NOAEL dose 2500 **>> Unit used** mg/kg-bw

>> Maternal NOAEL effect None.

>> Maternal Precision/LOAEL >

>> Maternal LOAEL dose 2500 **>> Unit used** mg/kg-bw

>> Maternal LOAEL effect None.

>> Developmental Precision/NOAEL =

>> Developmental NOAEL dose 2500 **>> Unit used** mg/kg-bw

>> Developmental NOAEL effect None.

>> Developmental Precision/NOAEL >

>> Developmental LOAEL dose 2500 **>> Unit used** mg/kg-bw

>> Developmental LOAEL effect None.

>> Actual dose

As above.

>> Maternal data with dose level (with NOAEL value).

See results

>> Fetal data with dose level (with NOAEL value).

See results

>> Statistical results

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation		Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-		Study Number	3
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)		Completed:	

See results

Results Remark

In dams, TBBPA did not affect the rate of pregnancy or parturition. In fetuses, TBBPA did not induce embryo/fetal toxicity, and no external, skeletal or visceral anomalies were detected. No adverse change was observed in the postnatal development (21 days post birth) of the offspring of any group.

Conclusions

The maternal, fetal and neonatal NOAEL was 2,500 mg TBBPA /kg/d, the highest dose tested.

Data Quality

Reliability Reasonable.

Data Reliability Remarks

The publication is written in Japanese, with only the data tables and abstract available in English. The lack of toxicity in this study at 2,500 mg/kg-bw is consistent with the 2001 BFRIP study.

Reference

>> Remarks

Noda, T., Morita, S., Ohgaki, S., Shimizu, M. And Yamada, A. Safety evaluation of chemicals for use in house-hold products (VII) - teratological studies on tetrabromobisphenol A in rats. 1985. Annual Report, 48, pp 106-12. Osaka City Institute of Public Health and Environmentgal Sciences.

General

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation	Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-	Study Number	4
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)	Completed:	N

Revision Date: 12/14/01

Test Substance

Remarks: Tetrabromo-bis-phenol A, purchased from Aldrich and recrystallized from chloroform.

Chemical Category

Method

>> Method/Guideline followed

Other

>> GLP: No

>> Year study performed: 1998

>> Species

mice

>> Strain | **Mammal strai:** NMRI

>> Sex: M

>> Number of males per dose: 0 | **>> Number of females per dose:** 0

>> Route of Administration: Oral

>> Days of Gestation:

>> Frequency of treatment: single dose on postnat

>> Doses: 0.75 and 11.5 mg

>> Control Group: Yes | **Concurrent control**

>> Statistical Method

ANOVA. Pairwise testing between treated and control groups: Tukey's honestly signficant difference test.

Remarks for Method

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation	Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-	Study Number	4
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)	Completed:	N

Methodology developed by the paper's authors. TBBPA (0.75 or 11.5 mg) was administered as a single oral dose to neonatal mice (n=8) on postnatal day 10. The vehicle was a 20% fat emulsion.

At 2 and 4 months of age, the mice were evaluated for spontaneous behavior: locomotion (horizontal movement), rearing (vertical movement) and total activity (all types of vibration within the test cage, e.g. those caused by mouse movements and grooming).

At 5 months of age, the mice were evaluated in a swim maze (Morris water maze type). The mice's ability to find a submerged platform was studied for 5 days.

Results

>> Maternal Precision/NOAEL

>> Maternal NOAEL dose 0 **>> Unit used**

>> Maternal NOAEL effect

>> Maternal Precision/LOAEL

>> Maternal LOAEL dose 0 **>> Unit used**

>> Maternal LOAEL effect

>> Developmental Precision/NOAEL

>> Developmental NOAEL dose 0 **>> Unit used**

>> Developmental NOAEL effect

>> Developmental Precision/NOAEL

>> Developmental LOAEL dose 0 **>> Unit used**

>> Developmental LOAEL effect

>> Actual dose

As described above.

>> Maternal data with dose level (with NOAEL value).

>> Fetal data with dose level (with NOAEL value).

EPA High Production Volume (HPV) Track

Toxicity End Point:
Developmental Toxicity/Teratogenicity

Sponsor ID	[redacted]	Albemarle Corporation	Create Date	2/6/01
CAS Number	79947	Phenol, 4,4'-isopropylidenebis[2,6-dibromo-	Study Number	4
Consortia ID	[redacted]	CMA Brominated Flame Retardant Industry Panel (BFRIP)	Completed:	N

>> Statistical results

See results.

Results Remark

No clinical signs of toxicity. No effect on weight gain.

TBBPA (0.75 or 11.5 mg) administered as a single dose orally on postnatal day 10 had no effect on spontaneous behavior or swim maze performance in mice tested at 2, 4 or 5 months of age.

Conclusions

TBBPA (0.75 or 11.5 mg) administered as as a single dose orally on postnatal day 10 had no effect on spontaneous behaviour or swim maze performance in mice tested at 2, 4 or 5 months of age.

Data Quality

Reliability unknown

Data Reliability Remarks

This is a nonstandard test. The reliability and reproducability of the results are unknown.

Reference

>> Remarks

Eriksson, P., Jakobsson, E., and Fredriksson, A. 1998. Developmental neurotoxicty of brominated flame retardants, polybrominated diphenyl ethers and tetrabromo-bis-phenol A. Organohalogen Compounds, Vol. 35, pp. 375-377.

Eriksson, P., Jakobsson, E., and Fredriksson, A. 2001. Brominated Flame Retardants: A novel class of developmental neurotoxicants in our environment? Environmental Health Perspectives, 109, 9, 903-908.

General

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